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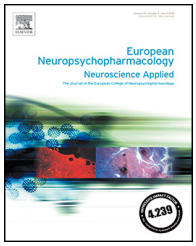

The affinity of antipsychotic drugs to dopamine and serotonin 5-HT$_2$ receptors determines their effects on prefrontal-striatal functional connectivity

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Abstract
One of the major challenges of cross-species translation in psychiatry is the identification of quantifiable brain phenotypes linked to drug efficacy and/or side effects. A measure that has received increasing interest is the effect of antipsychotic drugs on resting-state functional connectivity (FC) in magnetic resonance imaging. However, quantitative comparisons of antipsychotic drug-induced alterations of FC patterns are missing. Consideration of receptor binding affinities provides a means for the effects of antipsychotic drugs on extended brain networks to be related directly to their molecular mechanism of action. Therefore, we examined the

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relationship between the affinities of three second-generation antipsychotics (amisulpride, risperidone and olanzapine) to dopamine and serotonin receptors and FC patterns related to the prefrontal cortex (PFC) and striatum in Sprague-Dawley rats. FC of the relevant regions was quantified by correlation coefficients and local network properties. Each drug group (32 animals per group) was subdivided into three dose groups and a vehicle control group. A linear relationship was discovered for the mid-dose of antipsychotic compounds, with stronger affinity to serotonin 5-HT_{2A}, 5-HT_{2C} and 5-HT_{1A} receptors and decreased affinity to D_3 receptors associated with increased prefrontal-striatal FC ($p = 0.0004$, $r^2 = 0.46$; $p = 0.004$, $r^2 = 0.33$; $p = 0.002$, $r^2 = 0.37$; $p = 0.02$, $r^2 = 0.22$, respectively). Interestingly, no correlation was observed for the low and high dose groups, and for D_2 receptors. Our results indicate that drug-induced FC patterns may be linked to antipsychotic mechanism of action on the molecular level and suggest the technique's value for drug development, especially if our results are extended to a larger number of antipsychotics.

1. Introduction

Resting state functional magnetic resonance imaging (rs-fMRI) has been increasingly used to explore the neurobiological effects of pharmacological compounds on functional connectivity (FC) within brain networks (Gass et al., 2016; Hoflich et al., 2015; Nasrallah et al., 2014; Scheidegger et al., 2012; Shah et al., 2016). To help bridge the "valley of death" in psychiatric drug development, such advanced techniques have become incorporated in early stages of psychopharmaceutical research (Artigas et al., 2017; Khalili-Mahani et al., 2017; Millan et al., 2015). As a result, rs-fMRI has begun to be used in drug development to demonstrate functional effects of novel compounds, and can complement measures of direct target engagement obtained from positron emission tomography (PET) (Smucny et al., 2014).

Effects of various antipsychotics on FC in the rat have been investigated and related to previously known or anticipated behavioral modifications, receptor-binding affinities and typical side effects (Gass et al., 2013; Preece et al., 2001). Direct comparisons of more than one compound have been qualitatively described and depicted for antipsychotics and other substances (Schwarz et al., 2007a, b; Shah et al., 2016). Agonist-antagonist designs have been investigated (Nasrallah et al., 2014) as well as pharmacologically induced models of psychiatric diseases and their response to pharmaceutical intervention (Schwarz et al., 2007c). However, direct comparisons of drug effects on FC patterns have, to date, been essentially qualitative. A framework linking network-level FC effects to the underlying molecular mechanisms of action would enable a more meaningful interpretation of FC experiments and increase their value in the development of new treatments.

The effects of many currently available antipsychotics are thought to be mediated via subtypes of dopamine and serotonin receptors. Selective dopamine receptor type 2 (D_2) antagonism, as found in first generation antipsychotics such as haloperidol, is considered to alleviate positive symptoms related to increased presynaptic synthesis and release of dopamine in the striatum (Howes and Kapur, 2009). Additional antagonism or inverse agonism at serotonin 5-HT_2 receptors has been introduced to antipsyhotics' profiles in an attempt to mitigate extrapyramidal motoric side effets of antipsychotic treatment and to potentially inrease their efficacy for the treatment of negative and cognitive symptoms (Kusumi et al., 2015; Leucht et al., 2009).

While reports of antipsychotic drug-induced FC patterns are beginning to emerge in both man and rodent (Gass et al., 2013; Hadley et al., 2014; Kraguljac et al., 2016; Sarpal et al., 2015), systematic studies of the relationship between these connectivity effects and the receptor binding affinities of different second-generation antipsychotics (SGAs) have not yet been reported. Meta-analyses indicate that SGAs amisulpride, olanzapine and risperidone are more efficacious compared to first-generation antipsychotics (Davis et al., 2003; Leucht et al., 2009). We performed a head-to-head, dose-response comparison of the effects of these three compounds on FC in the rat brain, and examined the relationship betweeen their FC effects and their serotonin and dopamine receptor affinities. Since striatum and prefrontal cortex (PFC), among further regions, exhibit high density of D_2- and 5-HT_{2A} receptors, respectively (Gurevich and Joyce, 1999; Pompeiano et al., 1994), and are thought to be strongly implicated in the pathophysiology of schizophrenia, we specifically explored rs-FC in these two regions. Prior imaging studies have indicated alterations in striatal and prefrontal connectivity (Preece et al., 2001; Sarpal et al., 2015).

We hypothesized that FC between PFC and striatum would be differentially affected depending on anti-dopaminergic and anti-serotonergic properties of the respective antipsychotic drugs, with atypical antipsychotic properties being associated with stronger FC.

2. Experimental procedures

2.1. Animals and compounds

This experiment comprised three sub-studies, in each of which a single antipsychotic compound (risperidone, olanzapine or amisulpride) was tested at three dose levels ($N = 8$ animals per group) versus a vehicle control group ($N = 8$). Each administration comprised a single, acute dose of the active compound or vehicle. Since the presented data have been acquired in a parallel group design, an intra-subject correction to a baseline condition devoid of

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